Effect of hypoxia and hyperoxia on exercise performance in healthy individuals and in patients with pulmonary hypertension: A systematic review

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Abstract: Exercise performance is determined by oxygen supply to working muscles and vital organs. In healthy individuals, exercise performance is limited in the hypoxic environment at altitude, when oxygen delivery is diminished due to the reduced alveolar and arterial oxygen partial pressures. In patients with pulmonary hypertension, exercise performance is already reduced near sea level due to impairments of the pulmonary circulation and gas exchange and, presumably, these limitations are more pronounced at altitude. In studies performed near sea level in healthy subjects as well as in patients with pulmonary hypertension (PH) maximal performance during progressive ramp exercise and endurance of submaximal constant load exercise were substantially enhanced by breathing oxygen-enriched air. Both in healthy individuals and in PH-patients these improvements were mediated by a better arterial, muscular and cerebral oxygenation along with a reduced sympathetic excitation, as suggested by the reduced heart rate and alveolar ventilation at submaximal isoloads, and an improved pulmonary gas exchange efficiency, especially in patients with PH. In summary, in healthy individuals and in patients with pulmonary hypertension, alterations in the inspiratory PO2 by exposure to hypobaric hypoxia or normobaric hyperoxia reduce or enhance exercise performance, respectively, by modifying oxygen delivery to the muscles and the brain, by effects on cardiovascular and respiratory control and by alterations in pulmonary gas exchange. The understanding of these physiologic mechanisms helps counselling individuals planning altitude or air travel and prescribing oxygen therapy to patients with pulmonary hypertension.

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Effect of hypoxia and hyperoxia on exercise performance in healthy individuals and in patients with pulmonary hypertension: a systematic review

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Ulrich S, Schneider SR, Bloch KE. Effect of hypoxia and hyperoxia on exercise performance in healthy individuals and in patients with pulmonary hypertension: a systematic review. *J Appl Physiol* 123: 1657–1670, 2017. First published August 2, 2017; doi:10.1152/japplphysiol.00186.2017.—Exercise performance is determined by oxygen supply to working muscles and vital organs. In healthy individuals, exercise performance is limited in the hypoxic environment at altitude, when oxygen delivery is diminished due to the reduced alveolar and arterial oxygen partial pressures. In patients with pulmonary hypertension (PH), exercise performance is already reduced near sea level due to impairments of the pulmonary circulation and gas exchange, and, presumably, these limitations are more pronounced at altitude. In studies performed near sea level in healthy subjects, as well as in patients with PH, maximal performance during progressive ramp exercise and endurance of submaximal constant-load exercise were substantially enhanced by breathing oxygen-enriched air. Both in healthy individuals and in PH patients, these improvements were mediated by a better arterial, muscular, and cerebral oxygenation, along with a reduced sympathetic excitation, as suggested by the reduced heart rate and alveolar ventilation at submaximal isoloads, and an improved pulmonary gas exchange efficiency, especially in patients with PH. In summary, in healthy individuals and in patients with PH, alterations in the inspiratory P_{O_2} by exposure to hypobaric hypoxia or normobaric hyperoxia reduce or enhance exercise performance, respectively, by modifying oxygen delivery to the muscles and the brain, by effects on cardiovascular and respiratory control, and by alterations in pulmonary gas exchange. The understanding of these physiological mechanisms helps in counselling individuals planning altitude or air travel and prescribing oxygen therapy to patients with PH.

exercise; hyperoxia; hypoxia; pulmonary hypertension

INTRODUCTION

Exercise performance is determined by the oxygen supply to working muscles and vital organs, including the brain (43). Maximal exercise performance and oxygen uptake ($\dot{V}_{O_2}$) are reduced in the hypoxic environment at altitude or with simulated hypobaric or normobaric hypoxia (46, 63). On the other hand, oxygen-enriched air [normobaric hyperoxia, increased fraction of inspired oxygen ($F_{I_{O_2}}$)] may enhance exercise performance in healthy individuals and, potentially to an even higher extent, in patients with respiratory diseases associated with exercise-induced hypoxemia, such as pulmonary hypertension (PH) (12). Thus studies on the effect of breathing oxygen-enriched air near sea level on exercise performance in healthy individuals and in patients with respiratory disease may help to identify mechanisms involved in exercise limitation in normoxia and in the hypoxic environment at altitude.

The purpose of the present work is, therefore, to review the physiological effects of hypobaric or normobaric hypoxia and of normobaric hyperoxia on exercise performance in healthy subjects and in patients with PH as an example of a group of cardiorespiratory diseases associated with impaired pulmonary gas exchange and circulation. The mini-review is based on a systematic analysis of the literature to identify potential therapeutic targets and areas of future research.

EFFECT OF HYPOXIA ON EXERCISE PERFORMANCE IN HEALTHY INDIVIDUALS

Exercise performance is determined by oxygen delivery to the muscles by the cardiorespiratory system, the diffusion of oxygen from the capillaries into the cells, and the utilization of oxygen by the skeletal muscles (2). At higher exercise intensity, the oxygen supply by the cardiorespiratory system may not meet the metabolic demand, and accumulation of H^+ and inorganic phosphates at the neuromuscular junction and in the muscle cell limit contractility and induce fatigue (1, 3). The simultaneously increasingly inadequate oxygen delivery to the brain has been

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suggested to limit exercise by cessation of central command to the locomotor system (4, 41, 44).

Exposure to hypobaric hypoxia at altitude challenges the oxygen delivery system to organs at rest and even more during exercise, when skeletal muscular oxygen demand substantially increases. Acute exposure to high altitude induces an increase in ventilation and heart rate, mainly driven by hypoxemia-induced carotid chemoreceptor activation, sympathoexcitation, and vagal withdrawal (Fig. 1) (38, 56). The heart rate-mediated initial increase in cardiac output compensates for the decrease in arterial oxygen content, so that the product of both, the systemic oxygen delivery, remains unchanged at rest (38, 56). With sojourns at altitude over several days, the resting cardiac output normalizes through a decrease in stroke volume, which is attributed to a hypoxia-induced reduction in plasma volume and thus lower left ventricular end-diastolic volume (55). Ventilation and heart rate, however, remain increased even after acclimatization mediated by a sustained sympathetic response driven by peripheral chemoreceptors sensitized by the persistent hypoxemia (25, 26, 33). Under exercise, these adaptive mechanisms are additionally stressed, and performance is, therefore, limited in the hypoxic environment at altitude. Several studies have described a decreased maximal workload (W_{max}) and $\dot{V}O_2$ associated with decreasing barometric pressure and alveolar partial pressure of oxygen ($P_{A_{O_2}}$) (79, 81). Thus exercise at altitude is associated with a sustainably elevated respiratory rate and consecutively increased minute ventilation ($\dot{V}E$), even more upon acclimatization, which improves the arterial O_2 saturation from pulse oximetry (Sp_{O_2}), but is associated with a lower arterial P_{CO_2} and higher ventilatory equivalents for $\dot{V}O_2$ and CO_2 output ($\dot{V}CO_2$) ($\dot{V}E/\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$, respectively), indicating ventilatory inefficiency (Figs. 2 and 3) (26). During exercise at lowland, hyperpnea allows healthy individuals to maintain a sufficiently high $P_{A_{O_2}}$ that, together with flow-induced increased pulmonary vessel recruitment and distention, ensures an adequate diffusion of oxygen through the alveolar membrane, thereby preventing exercise-induced hypoxemia through diffusion limitation, except for highly trained athletes at very high work levels. At altitude, the lower inspiratory P_{O_2} and, consequently, the reduced arterial P_{O_2} ($P_{A_{O_2}}$) stimulate ventilation. At which level of hypobaric hypoxia the associated increasingly high energy cost of breathing eventually outweighs the hyperventilation-induced increased oxygen availability, and thus limits exercise performance, has not been exactly determined by experimental evidence (7, 75, 80). Systemic availability of oxygen during exercise at altitude is additionally hampered by limitation of the alveolar-arterial oxygen diffusion due to an increased cardiac output, which shortens the pulmonary capillary blood transit time, thus precluding equilibration of the pulmonary capillary P_{O_2} with the reduced $P_{A_{O_2}}$ (73). Thus, despite alveolar microvascular recruitment by the enhanced cardiac output and associated increased pulmonary capillary blood volume, the oxygen loading onto hemoglobin at any given cardiac output is reduced in hypoxia compared with normoxia, and the arterial oxygen saturation, therefore, declines at a lower cardiac output. The relative increase of the cardiac output during exercise at altitude compared with sea level is not clear. Studies revealed that, with acute exposure to hypoxia, the cardiac output was increased at low workloads, along with a higher heart rate, which was attributed to a combined inhibition of β-adrenergic and muscarinic receptors (57). At altitude, the maximal work rate, the maximal $\dot{V}O_2$ ($\dot{V}O_{2max}$), heart rate, and cardiac output were all decreased in comparison to sea level (12, 74), whereas there was little change in the relationship between these variables (38, 49). Whether the reduced maximal cardiac output at altitude is a cause or consequence of the decreased $\dot{V}O_2$ remains uncertain (73).

Hypoxia induces pulmonary vasoconstriction, an adaption that reduces ventilation-perfusion mismatch and optimizes the lung diffusion and perfusion matching (8, 36). But exercise in the hypoxic environment is associated with a deterioration of ventilation-perfusion matching, which is only partly corrected by hypoxic vasoconstriction (36). Thus it is thought that the increase in pulmonary arterial pressure (PAP) induced by hypoxic pulmonary vasoconstriction, together with the exercise-induced increase in blood flow, contributes to gas exchange deterioration during exercise at altitude, although there

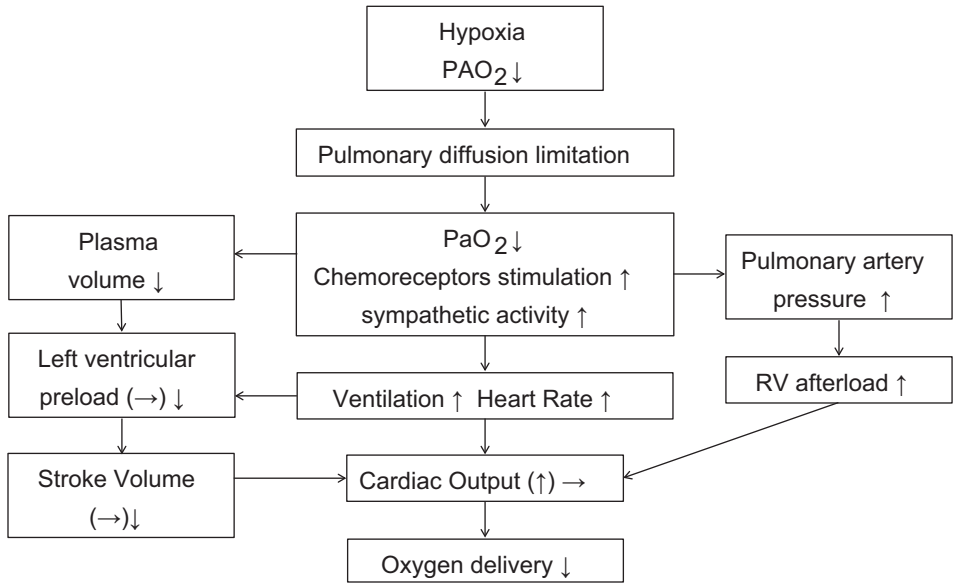

Fig. 1. Main adaptive mechanisms to exercise under acute exposure to hypobaric hypoxia at altitude or simulated hypoxia with hypoxic air mixtures are shown. Feedback loops in between mechanisms are not shown, but play additional roles.

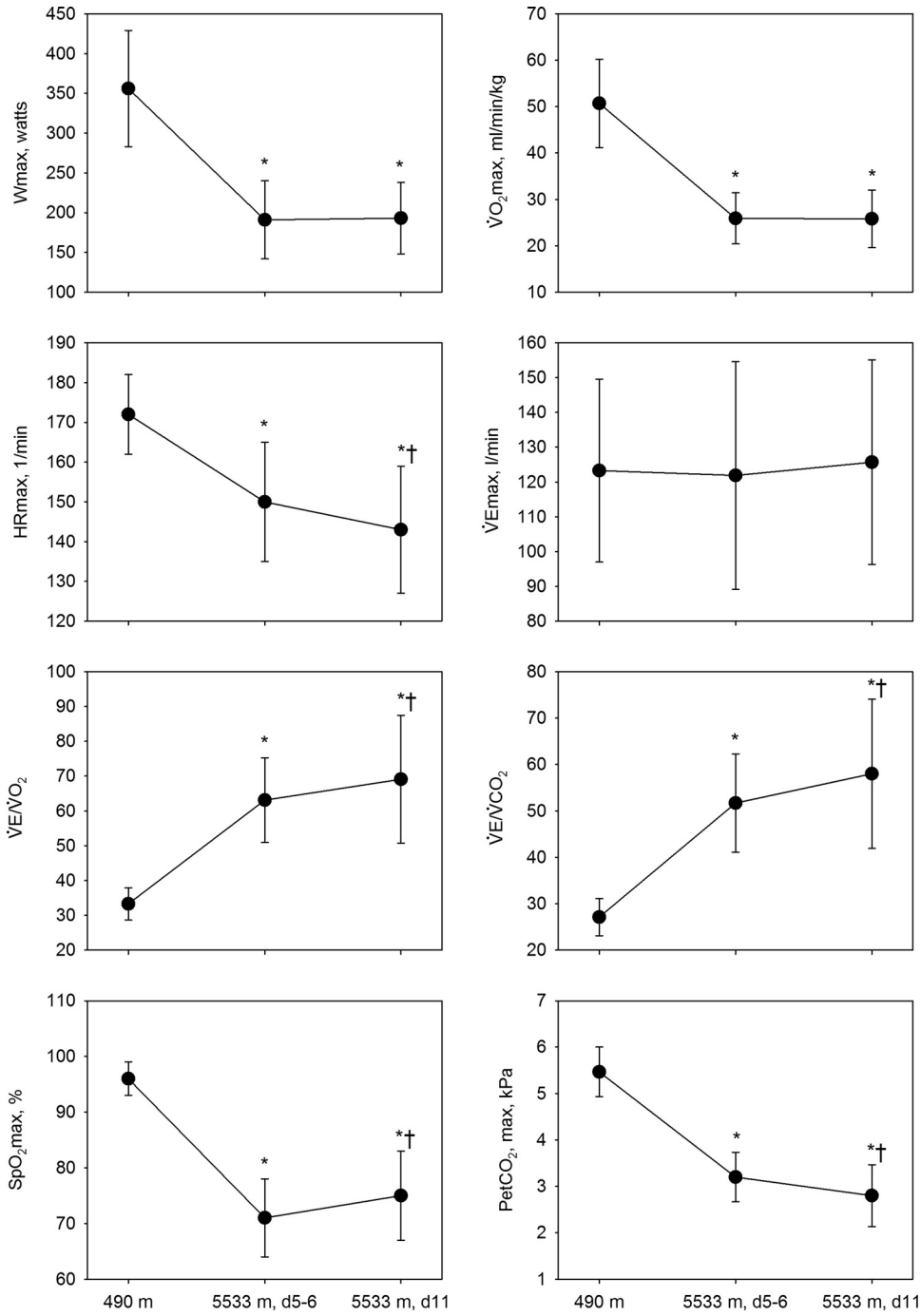

Fig. 2. Data from maximal cycle exercise in 32 mountaineers studied near sea level (490 m) and after staying for 5–6 and 11 days at an altitude of 5,533 m. Maximal values for work rate (W_{max}), oxygen uptake ($\dot{V}O_{2max}$), heart rate (HR_{max}), minute ventilation ($\dot{V}E_{max}$), ventilatory equivalents ($\dot{V}E/\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$), pulse oximetry (Sp_{O_2}), and end-tidal P_{CO_2} ($P_{ET_{CO_2}}$) are shown. *$P < 0.05$ vs. 490 m. †$P < 0.05$ vs. *day 5–6* at 5,533 m. Data were derived from a study by Latshang et al. (26).

is a high interindividual variability in this response (34, 75). Hypoxic pulmonary vasoconstriction, combined with a decreased pulmonary vascular distensibility, results in a steep pressure/flow relationship during exercise, which, combined with hypoxemia, contributes to limitations in performance at altitude (50, 51). Studies showing that reduction of pulmonary vascular resistance by phosphodiesterase inhibitors or endothelin-receptor antagonists is associated with an increased $\dot{V}O_2$ and exercise capacity at altitude and in normobaric hypoxia support the notion that an increased right ventricular afterload contributes to exercise limitation at altitude (13, 15, 19). However, the interindividual contribution of this mechanism to exercise limitation at altitude may vary considerably (34, 75).

As resting cardiac output returns to baseline within 1–2 wk of acclimatization, even before the onset of polycythemia, an increased cellular oxygen extraction has been postulated (38, 56), and this should be especially pronounced during exercise to match the heightened oxygen demand of exercising muscles. However, absolute oxygen extraction at rest and during peak exercise were decreased in five subjects after 5–6 days at an altitude of 4,559 m, with an unchanged oxygen extraction ratio (i.e., an unchanged ratio of arterial-venous oxygen content to

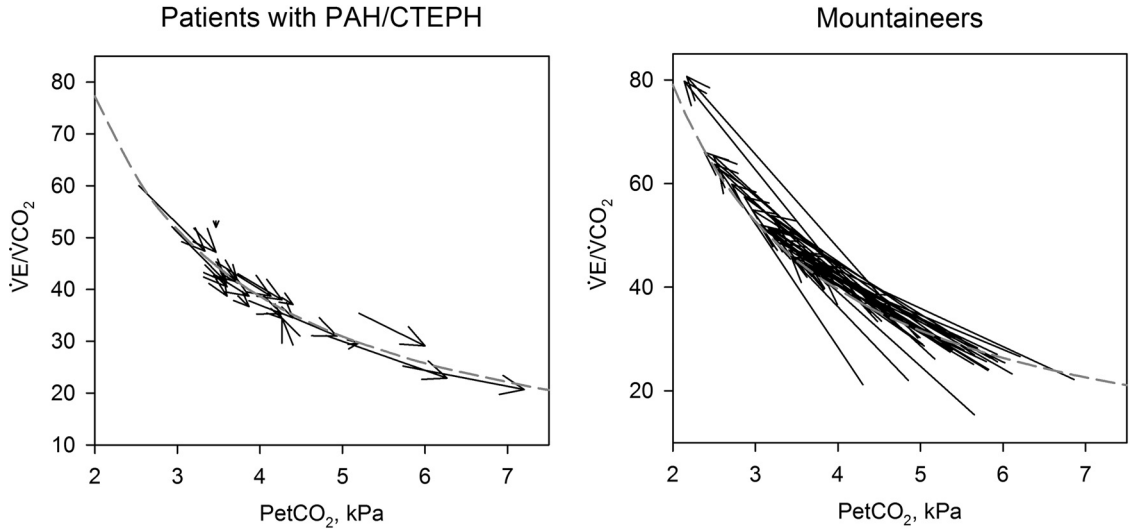

Fig. 3. Both hypoxia due to impaired pulmonary gas exchange in patients with pulmonary hypertension and environmental hypoxia in mountaineers similarly induce ventilatory inefficiency. Plots of $\dot{V}E/\dot{V}CO_2$ vs. $P_{ET_{CO_2}}$ during maximal cycle exercise in patients with PAH/CTEPH [*left*, data derived from Ulrich et al. (69)] and healthy mountaineers [*right*, data derived from Latshang et al. (26)] are shown. *Left*: in PAH/CTEPH patients, lines start with values measured during ambient air breathing ($F_{I_{O_2}}$ 0.21) near sea level and end in arrows representing values measured during breathing oxygen-enriched air ($F_{I_{O_2}}$ 0.5). *Right*: in mountaineers, lines start with values measured at an altitude of 490 m and end in arrows measured on *day 5–6* after ascent to an altitude of 5,533 m. Hyperoxia in patients induced changes to the right along the line representing the rearranged alveolar gas equation (dashed shaded line), i.e., toward a greater ventilatory efficiency. In mountaineers, exposure to hypoxia at high altitude induces changes in the opposite direction, i.e., toward a greater ventilatory inefficiency. Mechanisms of acclimatization in mountaineers and physiological adaptations to long-term hypoxia that take place in PH patients are not represented.

arterial oxygen content) (35). Responsible factors might include a limited tissue oxygen diffusion due to the reduced Pa_{O_2} (72), a localized mismatch between oxygen demand and microcirculatory blood flow, an alteration in mitochondrial function, or a redistribution of blood flow between organs (27). Further research is warranted to clarify changes in regional and global oxygen extraction with altitude exposure.

Every physical activity starts with activation of the cerebral motor cortex with consecutive temporal and spatial recruitment of muscular units and ends with de-recruitment. Exercise is centrally perceived by motor-sensory neuronal connections that induce a sense of effort. When negative senses outweigh the positive ones, exercise is volitionally terminated. Despite the undoubted importance of these sensory aspects, they are not widely appreciated due to their subjective nature (23). However, which factors provide the input to the brain to stop exercise? While these factors are likely to be the same at low and high altitude, the hypoxic environment potentially alters their relative importance or processing (41). At the end of exercise at extreme altitude with a Pa_{O_2} of 26 Torr, subjects were almost unconscious, but rated their breathlessness similarly as high as their leg discomfort, despite no metabolic fatigue (18). This observation may indicate that the exhausting respiratory system limits the motor system via inhibition of locomotor drive by the brain, whereas muscle metabolism does not seem to be limiting (24, 53).

The studies discussed so far have provided insights into some pulmonary, cardiovascular, muscular, and cerebral mechanisms of adaptation and limitation of exercise performance under hypoxia (either hypobaric at altitude or normobaric at sea level). However, the interpretation of the findings has to account for weaknesses in the methods and design of these mostly uncontrolled case studies performed in a small number of mountaineers or athletes. In a systematic analysis of the literature cited in PubMed (see APPENDIX A; search terms and inclusion/exclusion criteria are detailed in Table A1), including at least eight participants, we found five randomized-controlled trials providing data on the effects of hypobaric hypoxia, normobaric hypoxic gas mixtures, or altitude exposure on exercise capacity quantified by W_{max} or $\dot{V}O_2$ (Tables A1 and A2). Two of the studies were crossover trials in hypobaric chambers (altitude equivalent of 3,800 m and up to 2,286 m) (60, 71), where subjects were blinded to the chamber pressure, a third was a field study in Indian soldiers (58), which were randomized to exercise near sea level or after 4 wk of acclimatization to 4,560 m, and two used normobaric hypoxia (9, 16). All studies showed a decreased exercise performance in $\dot{V}O_{2max}$ under hypoxia compared with ambient air near sea level. Furthermore, well-designed studies with modern methodology are warranted to study the mechanisms of exercise limitation in hypoxia.

EFFECT OF HYPEROXIA ON EXERCISE PERFORMANCE IN HEALTHY INDIVIDUALS

Researchers have addressed the question of whether breathing oxygen-enriched air (normobaric hyperoxia) would improve exercise performance. Various studies with different $F_{I_{O_2}}$ values and exercise modalities, mostly including a limited number of trained athletes, revealed conflicting results, but generally found an enhanced performance with hyperoxia. For example, Wilson et al. (82) have shown that progressively increasing $F_{I_{O_2}}$ values were associated with dose-dependent increases in running endurance of healthy subjects at 110% of $\dot{V}O_{2max}$. $\dot{V}E$ was significantly decreased, whereas the maximal heart rate was similar in different $F_{I_{O_2}}$ conditions. In other investigations, a decreased lactate accumulation under hyperoxia compared with normoxia was found at submaximal exercise intensities (50–70% of peak $\dot{V}O_2$), despite a prolonged

performance (29, 30). Further studies in a limited number of mostly healthy young athletes found an unchanged or increased maximal performance with higher $F_{I_{O_2}}$ (22, 42, 45).

We recently studied the effect of breathing oxygen-enriched air ($F_{I_{O_2}}$ 0.5) vs. ambient air ($F_{I_{O_2}}$ 0.21) in 32 healthy subjects near sea level (460 m). They performed two exhaustive progressive ramp and two constant-load cycle cardiopulmonary exercise tests (CPET), each under $F_{I_{O_2}}$ 0.5 and $F_{I_{O_2}}$ 0.21, according to a randomized, sham-controlled crossover trial (68). We found that breathing oxygen-enriched air increased the maximal power output by 5.3% and endurance time in constant-load CPET at 75% of the $\dot{V}O_{2max}$ by 52%. The higher maximal work rate in progressive ramp exercise with hyperoxia compared with normoxia was associated with an improved arterial, muscle and cerebral tissue oxygenation (CTO measured by near-infrared spectroscopy) with a postponed CTO decline. In addition, heart rate, $\dot{V}E$, and ventilatory equivalents for $\dot{V}CO_2$ and $\dot{V}O_2$ at submaximal isoloads were reduced (Fig. 4). Since the end-tidal PCO_2 ($P_{ET_{CO_2}}$) was increased in hyperoxia compared with normoxia, these findings are consistent with a reduction in peripheral chemoreceptor sensitivity by hyperoxia with relative reduction in alveolar ventilation and a rise in the alveolar PCO_2 (and, hence, $P_{ET_{CO_2}}$) (12). The higher CTO with postponed drop toward end-exercise under hyperoxia may suggest a role of the brain in exercise limitation (42, 66, 68). The higher $\dot{V}O_2$ under hyperoxia is not entirely understood, but may be related in part to changes in metabolism, redistribution of blood flow, differences in type and recruited muscle fibers, and in metabolism of nonexercising tissues (47, 48, 68), Higher blood lactate levels due to increased exercise under hyperoxia seem not to play a role (14).

In summary, oxygen-enriched air improves maximal work rate and submaximal endurance time in healthy individuals through a better arterial and cerebral oxygenation associated with an enhanced ventilatory efficiency. In a systematic review of the literature, we identified four randomized-controlled trials, which included a least eight subjects and provided data on the effect of hyperoxia vs. normoxia air on maximal exercise performance in terms of workload or $\dot{V}O_2$ (Table A2). All revealed an increased workload of $\dot{V}O_2$ under hyperoxia (20, 42, 48, 68).

EFFECT OF HYPOBARIC HYPOXIA ON EXERCISE PERFORMANCE IN PATIENTS WITH PH

Precapillary PH is a condition hemodynamically defined as mean PAP $\geq$ 25 mmHg, along with a pulmonary arterial wedge pressure $\leq$ 15 mmHg. In the absence of relevant lung disease, the main forms are pulmonary arterial hypertension (PAH), which occurs in idiopathic form or in association with various diseases, or chronic thromboembolic PH (CTEPH) (17). The main symptom is exertional dyspnea, which is typically associated with oxygen desaturation, and leads to reduced quality of life (59). In terms of lung function, the

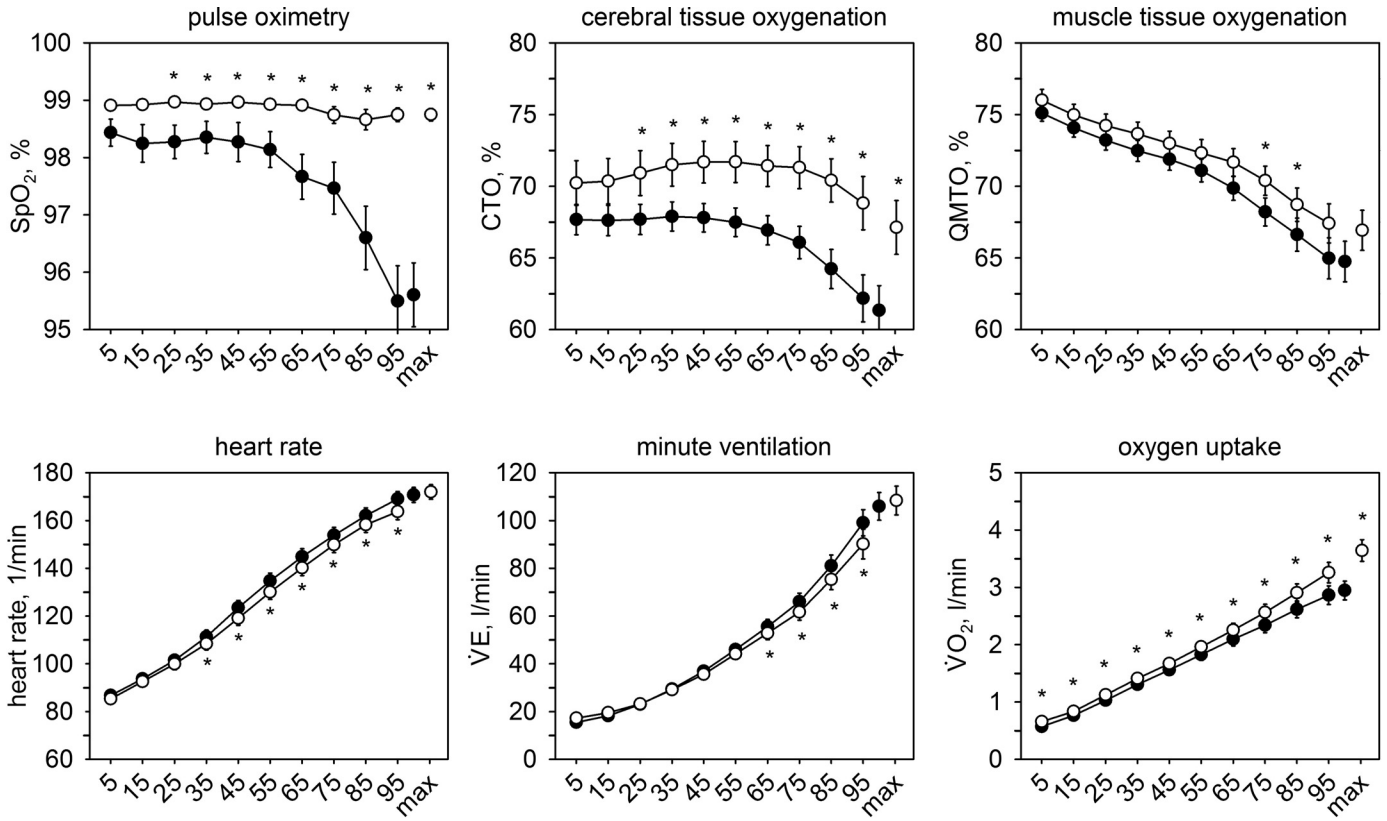

Fig. 4. Effect of hyperoxia on exercise performance in 32 healthy subjects (68). Physiological variables during progressive ramp exercise are represented by open circles for hyperoxia ($F_{I_{O_2}}$ 0.5) and by solid circles for normoxia ($F_{I_{O_2}}$ 0.21). Values are means ± SE over successive deciles of the maximal workload (W_{max}) achieved under normoxia; i.e., the value of 5 (*x*-axis) represents the mean over the range of 1–10% of W_{max} normoxia, etc. The last values represent means over the final 15 s of maximal exercise in hyperoxia and normoxia. *$P < 0.05$ for comparison of hyperoxia, $F_{I_{O_2}}$ 0.50, vs. normoxia, $F_{I_{O_2}}$ 0.21. QMTO, quadriceps muscle tissue oxygenation.

characteristic alteration in patients with PAH/CTEPH is a reduction in diffusing capacity while lung volumes are generally within normal limits (69). Exposure to hypobaric hypoxia at altitude or during air flights increases PAP through hypoxic pulmonary vasoconstriction already in healthy individuals and, presumably, even more in patients with PH due to their impaired hemodynamics and gas exchange (10, 34, 67). According to questionnaire assessments on flight experience, the percentage of PH patients perceiving symptoms during exposure to a moderately hypoxic environment like commercial air travel (with minimal cabin pressure equivalent to 2,437 m) is mostly small (64). Thus among 179 air passengers with stable PH, 46% of these were in New York Heart Association class II or IV, 3% reported dyspnea, 3% peripheral edema, 2% exhaustion, 1% each heart palpitations, chest pain, headache, worsening of condition, or fear of flying, and a total of 4% required a medical intervention; only 2% of the patients used supplemental oxygen during flights. In 34 PH patients flying at a mean altitude equivalent of 1,968 m on average during 3.6 h, there was a median drop in arterial oxygen saturation of 4.9% (range 2–16%) (52). However, of the 13 patients (38%) who reported symptoms during the flight, 5 (38%) also revealed desaturation. Since no serious adverse events were reported in this study, the clinical relevance of the findings remain elusive. An adverse effect of altitude exposure and occurrence of high-altitude pulmonary edema has been reported anecdotally in patients with PH associated with malformations, absence or occlusion of pulmonary arteries, or other rare PH forms (32). Prospective data on patients with PH exposed to real altitude in the mountains are lacking, so that most experts recommend against altitude sojourns in PH or, if necessary, to use supplemental oxygen (31). In the absence of conclusive evidence, current guidelines based on expert opinion recommend that PH patients in functional class III and IV or with a $Pa_{O_2} < 8$ kPa near sea level either avoid exposure to altitudes $\geq$1,500–2,000 m or use supplemental oxygen during altitude or air travel (17). A systematic review of the literature cited in PubMed did not reveal any randomized or prospective case series study evaluating effects of exposure to hypoxia on exercise performance in terms of maximal work rate or $\dot{V}O_2$ in patients with PAH/CTEPH. This lack of information may be related in part to concerns of investigators of letting patients with advanced PH perform strenuous exercise. Maximal exercise testing was found safe under normoxic condition in PH patients (21, 61, 76, 78). In our own experience, a few minutes at rest in normobaric hypoxia did not worsen hemodynamics in PH patients with mild to moderate disease (A. Groth, unpublished observations). However, the effect of hypoxia on pulmonary hemodynamics under exercise has not been studied, and the lack of hemodynamic impairment with normobaric hypoxia at rest cannot exclude that certain patients with severe disease might be at risk of right heart failure or even sudden cardiac death when performing strenuous exercise. Robust evidence of the potential risk of exercise and of exercise in hypoxia might help to counsel the increasing number of PH patients who desire to travel to high-altitude areas or to undergo air travel. Well-designed scientific studies that appropriately address safety concerns are, therefore, urgently needed.

EFFECT OF HYPEROXIA ON EXERCISE PERFORMANCE IN PATIENTS WITH PH

The exercise limitation and symptoms in patients with precapillary PH have been attributed to their impaired hemodynamics that lead to several pathophysiological consequences, with a crucial finding being hyperventilation at rest and an excessive ventilatory response to exercise, leading to high ventilatory equivalents for $\dot{V}CO_2$ ($\dot{V}E/\dot{V}CO_2$) and $\dot{V}O_2$ ($\dot{V}E/\dot{V}CO_2$) (62). The main underlying mechanisms are sympathetic overexcitation and increased chemosensitivity with hyperventilation-associated increased physiological dead space. Moreover, there is an inadequate increase in cardiac output during exercise, leading to a low mixed-venous and arterial oxygen saturation and early lactic acidosis that raises ventilatory requirements even further due to excessive CO_2 production (39, 65, 77). These mechanisms lead to arterial oxygen desaturation during exercise as a cardinal feature of PH with, consequently, reduced oxygen delivery to the muscles, the brain, and other organs, resulting in impaired exercise performance (28, 37). Thus it is comprehensible to hypothesize that breathing oxygen-enriched air during physical activity in daily life or during exercise training may improve performance in PH patients. Although resting hemodynamics as well as arterial tissue oxygenation and CTO improved in patients with PAH/CTEPH while breathing oxygen during right heart catheterization, the effect of hyperoxia on exercise performance had not been adequately studied until recently (37). Therefore, current guidelines recommending long-term oxygen therapy in PH patients with resting $Pa_{O_2} < 8$ kPa or in case of symptomatic benefit are not based on robust evidence (17). To address this point, our laboratory performed a randomized, sham-controlled trial demonstrating that nocturnal oxygen therapy in PAH/CTEPH patients with nocturnal oxygen desaturation improves not only sleep-disordered breathing, but also exercise capacity (i.e., the 6-min walk distance) and symptoms during daytime already after 1 wk (70). In recent further randomized trials in patients with PAH/CTEPH, our laboratory has found that breathing oxygen-enriched air (FI_{O_2} 0.50) compared with breathing ambient air (FI_{O_2} 0.21) significantly enhanced maximal work rate in cycling ramp exercise tests and substantially increased endurance in submaximal constant-load exercise (69). These improvements were associated with a higher Pa_{CO_2} at end-exercise and a reduced ratio of $\dot{V}E/\dot{V}CO_2$ (Fig. 3), whereas the dead physiological space-to-tidal volume ratio remained unchanged. This was consistent with a reduction in excessive ventilatory drive by hyperoxia that reduced the ventilatory requirement for $\dot{V}CO_2$ through an increase in the alveolar CO_2 fraction and, consequently, the PET_{CO_2} fraction. Breathing oxygen-enriched air was associated with a higher Pa_{O_2} and thus increased oxygen delivery to the tissues, resulting in a higher cerebral and quadriceps muscle tissue oxygen saturation, indicating a better availability of oxygen in working muscles and sensory and motoneurons, thus allowing higher intensities and prolonged exercise with less dyspnea perception.

A systematic review of the literature cited in PubMed did not identify any further randomized trials investigating the effect of breathing oxygen-enriched air on exercise performance in PAH/CTPEH, in addition to the ones described above (Table A2) (69).

THERAPEUTIC IMPLICATIONS AND FUTURE RESEARCH

The reduced exercise capacity in healthy individuals exposed to hypoxia can be increased by acclimatization (26), presumably by supplemental oxygen and, according to randomized-controlled trials, by pulmonary vasodilator drugs, such as endothelin receptor antagonists or phosphodiesterase-5 inhibitors or (in subjects susceptible to high-altitude pulmonary edema) by dexamethasone (19, 38, 40). Conversely, acetazolamide seems to reduce exercise capacity at altitude, despite a higher Sp_{O_2} at rest, although these data are not conclusive (5). Future studies are warranted to address the mode of actions of drugs that modify pulmonary hemodynamics, gas exchange, and control of breathing in healthy subjects. Moreover, a clinically important research question is whether these drugs would increase exercise capacity in the hypoxic environment also in patients with PAH/CTEPH or other respiratory diseases. Whether supplemental oxygen therapy in addition to current drugs would improve the capacity to perform daily activities or effectiveness of training in PAH/CTEPH patients with exercise-induced hypoxemia remains to be determined in future randomized trials (11). Further studies might investigate other potential therapeutic options, such as inhaled steroids, betamimetics, and other agents (6, 54).

CONCLUSIONS

Current evidence suggests that exposure to hypobaric or normobaric hypoxia impairs exercise capacity in healthy subjects by decreasing the inspiratory P_{O_2}, $P_{A}O_2$, and $P_{A_{O_2}}$, thereby reducing the availability of oxygen in working muscles, in the brain, and in other tissues. In patients with PH, the exercise performance is impaired already in normoxia and, presumably, even more so in hypoxic conditions. The main mechanisms of exercise limitation in PH are comparable to those in healthy individuals, but are even more pronounced at corresponding exercise levels.

Recent randomized trials indicate that normobaric hyperoxia achieved by breathing oxygen-enriched air increases exercise performance in healthy subjects and even more in PH patients. These improvements are mediated by a reduction of the ventilatory drive, allowing for a better ventilatory efficiency, and by an increased availability of oxygen in the working muscles and in the brain, leading to less dyspnea and a greater exercise tolerance. Future studies should address whether these acute improvements under hyperoxia would translate into an increased training effect or better daily performance of PH patients who are treated with supplemental oxygen at long term.

APPENDIX A: SYSTEMATIC SEARCH OF THE LITERATURE

A systematic search on the medical database PubMed (https://www.ncbi.nlm.nih.gov/pubmed/) was conducted from inception to January 31, 2017. The search strategy and the number of returned articles are listed below in Tables A1 and A2. Titles and abstracts of the returned articles were reviewed for the following inclusion criteria to select high-quality research: randomization to exercise under acute hypoxia or acute hyperoxia, a sample size of at least eight healthy subjects, and quantitative data on maximal exercise capacity and/or $\dot{V}_{O_2}$.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

S.U. conceived and designed research; S.U., S.R.S., and K.E.B. analyzed data; S.U. and K.E.B. interpreted results of experiments; S.U. and K.E.B. prepared figures; S.U. drafted manuscript; S.U. and K.E.B. edited and revised manuscript; S.U. and K.E.B. approved final version of manuscript.

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Table A1. *Systematic literature search and methods*

Topic	Search Terms	No. Returned Articles	No. Articles Fulfilling Selection Criteria
	Exercise under hypoxia in healthy individuals		
Altitude and exercise	{("random"[All Fields] AND "allocation"[All Fields]) OR "random allocation"[All Fields] OR random*[All Fields]} AND "altitude"[Ti] AND "exercise"[Ti] NOT animal*[All Fields] NOT training[Ti]	38	4
Hypoxia and exercise	{("random"[All Fields] AND "allocation"[All Fields]) OR "random allocation"[All Fields] OR random*[All Fields]} AND (hypobaric[Ti] OR "anoxia"[Ti] OR "hypoxia"[Ti]) AND "exercise"[Ti] NOT animal*[All Fields] NOT training[Ti]	89	1
Cardiopulmonary exercise testing and altitude	{("random"[All Fields] AND "allocation"[All Fields]) OR "random allocation"[All Fields]} AND ("cardiopulmonary exercise testing "[All Fields]) AND ("altitude"[All Fields]) NOT animal*[All Fields]	0	0
Cardiopulmonary exercise testing and hypobaric hypoxia	{("random"[All Fields] AND "allocation"[All Fields]) OR "random allocation"[All Fields]} AND ("cardiopulmonary exercise testing "[All Fields]) AND hypobaric[All Fields] AND ("anoxia"[All Fields] OR "hypoxia"[All Fields]) NOT animal*[All Fields]	0	0
	Exercise under hyperoxia in healthy individuals		
Hyperoxia and exercise	{("random"[All Fields] AND "allocation"[All Fields]) OR "random allocation"[All Fields]} AND (hyperoxi*[All Fields] OR "inspired fraction of oxygen"[All Fields] OR "supplemental oxygen"[All Fields] OR "supplementary oxygen"[All Fields]) AND "exercise"[All Fields] NOT animal*[All Fields]	3	1
Hyperoxia or increased FI_{O_2} and exercise	{("random"[All Fields] AND "allocation"[All Fields]) OR "random allocation"[All Fields]} AND (increas*FI_{O_2}[All Fields] OR hyperoxi*[All Fields] OR "inspired fraction of oxygen"[All Fields] OR "supplemental oxygen"[All Fields] OR "supplementary oxygen"[All Fields]) AND ("exercise"[All Fields]) NOT animal*[All Fields]	4	0
Hyperoxia and exercise	{("random"[All Fields] AND "allocation"[All Fields]) OR "random allocation"[All Fields] OR random*[All Fields]} AND (hyperoxi*[Ti] OR "inspired fraction of oxygen"[Ti] OR "supplemental oxygen"[Ti] OR "supplementary oxygen"[Ti]) AND "exercise"[Ti] NOT animal*[All Fields]	42	3
Hyperoxia and cardiopulmonary exercise test	{("random"[All Fields] AND "allocation"[All Fields]) OR "random allocation"[All Fields]} AND (exercise test[All Fields] OR "cpet"[All Fields]) AND (hyperoxi*[All Fields] OR "inspired fraction of oxygen"[All Fields] OR "supplemental oxygen"[All Fields] OR "supplementary oxygen"[All Fields]) NOT animal*[All Fields]	0	0
All	Total number of titles and abstracts screened	176	9
All	Number of articles containing maximal exercise data from altitude/hypoxia or hyperoxia studies on at least 8 healthy adult subjects		9
	Exercise under hypoxia or hyperoxia in patients with pulmonary arterial or chronic thromboembolic pulmonary hypertension		
Exercise and altitude and PAH or CTEPH	{(random[All Fields] AND allocation[All Fields]) OR "random allocation"[All Fields] OR random*[All Fields]} AND ("exercise test"[MeSH Terms] OR "cpet"[All Fields]) AND ("altitude"[MeSH Terms] OR "altitude"[All Fields]) AND ("precapillary pulmonary hypertension"[All Fields] OR "pulmonary arterial hypertension"[All Fields] OR "chronic thromboembolic pulmonary hypertension"[All Fields] OR IPAH[All Fields] OR PAH[All Fields] OR CTEPH[All Fields]) NOT animal*[All Fields]	1	0
Exercise and hypobaric hypoxia PAH or CTEPH	{(random[All Fields] AND allocation[All Fields]) OR "random allocation"[All Fields] OR random*[All Fields]} AND ("cardiopulmonary exercise testing "[MeSH Terms] OR " cardiopulmonary exercise testing "[All Fields]) AND hypobaric[All Fields] AND ("anoxia"[MeSH Terms] OR "anoxia"[All Fields] OR "hypoxia"[All Fields]) AND ("precapillary pulmonary hypertension"[All Fields] OR "pulmonary arterial hypertension"[All Fields] OR "chronic thromboembolic pulmonary hypertension"[All Fields] OR IPAH[All Fields] OR PAH[All Fields] OR CTEPH[All Fields]) NOT animal*[All Fields]	0	0
Hyperoxia and exercise and PAH or CTEPH	{"random allocation"[MeSH Terms] OR ("random"[All Fields] AND "allocation"[All Fields]) OR "random allocation"[All Fields] OR random*[All Fields]} AND ("precapillary pulmonary hypertension"[All Fields] OR hyperoxi*[All Fields] OR "inspired fraction of oxygen"[All Fields] OR "supplemental oxygen"[All Fields] OR "supplementary oxygen"[All Fields] OR "oxygen-enriched air"[All Fields]) AND ("exercise"[MeSH Terms] OR "exercise"[All Fields]) AND ("pulmonary arterial hypertension"[All Fields] OR "chronic thromboembolic pulmonary hypertension"[All Fields] OR IPAH[All Fields] OR PAH[All Fields] OR CTEPH[All Fields]) NOT animal*[All Fields]	3	1

Continued

Table 1.—*Continued*

Topic	Search Terms	No. Returned Articles	No. Articles Fulfilling Selection Criteria
CPET and hyperoxia and PAH or CTEPH	{"random allocation"[MeSH Terms] OR ("random"[All Fields] AND "allocation"[All Fields]) OR "random allocation"[All Fields] OR random*[All Fields]} AND ("cardiopulmonary exercise testing "[MeSH Terms] OR "cardiopulmonary exercise testing"[All Fields]) AND ("precapillary pulmonary hypertension"[All Fields] OR hyperoxi*[All Fields] OR "inspired fraction of oxygen"[All Fields] OR "supplemental oxygen"[All Fields] OR "supplementary oxygen"[All Fields] OR "oxygen-enriched air"[All Fields]) AND ("pulmonary arterial hypertension"[All Fields] OR "chronic thromboembolic pulmonary hypertension"[All Fields] OR IPAH[All Fields] OR PAH[All Fields] OR CTEPH[All Fields]) NOT animal*[All Fields]	0	0
All	Total number of titles and abstracts screened	4	1
All	Number of articles containing maximal exercise data from altitude or hyperoxia studies on at least 8 patients with PAH/CTEPH		1

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Table A2. *Outlines of randomized trials evaluating effects of hypoxia or hyperoxia on exercise performance in healthy subjects and patients with pulmonary artery or chronic thromboembolic pulmonary hypertension*

Reference	Design and Setting	EBM	*N*	Participants	Main Results	Comments
				Exercise under hypoxia in healthy individuals		
Van Cutsem et al. (71)	Design: Double-blinded, randomized crossover design. Exposure to hypoxia (0 m/3,800 m ASL equivalent) and thermal challenge (15/25°C). Setting: Hypobaric environmental chamber.	1b	9	Healthy male athletes (age 23 ± 3 yr)	Time at altitude: 2 times exposure to 3,800 m ASL within at least 1 wk for 2 h. Performance: In the control group (0 m, 15°C), subjects produced 434 ± 69 kJ in 30 min. The temperature group (0 m, 25°C) produced 420 ± 75 kJ, the altitude group (3,800 m, 15°C) 285 ± 48 kJ, and the altitude + temperature group (3,800 m, 25°C) 269 ± 47 kJ. Both altitude and higher temperature decreased exercise capacity with an additive effect.	
Dekerle et al. (9)	Design: Randomized crossover trial. Progressive ramp and constant-load bicycle exercise under normoxic (FI_{O_2} 0.21) and hypoxic (FI_{O_2} 0.15) conditions. Setting: Normobaric hypoxia altitude simulation (FI_{O_2} 0.15).	1b	11	Healthy subjects, 5 men, 6 women (age 35 ± 10 yr)	Time at altitude: Short-term exposure during exercise test in hypoxia. (FI_{O_2}: 0.15). Performance incremental ramp test: Normoxia (FI_{O_2} 0.21) vs. hypoxia (FI_{O_2} 0.15); W_{max} (294 ± 29 vs. 260 ± 30 W); P-$\dot{V}O_{2peak}$ (288 ± 30 vs. 259 ± 42 W); peak $\dot{V}O_2$ (3.50 ± 0.39 vs. 3.07 ± 0.45 l/min); peak heart rate (187 ± 11 vs. 179 ± 11 beats/min); resting Sp_{O_2} (98.5 ± 0.7 vs. 92.6 ± 4.2%); and end-exercise Sp_{O_2} (93.1 ± 3.1 vs. 81.5 ± 5.3%, $P < 0.05$). Performance constant workload: The following parameters did significantly differ among normoxia and hypoxia in the shortest as well as in the longest trial with $P < 0.01$: power output, 285 ± 34 vs. 249 ± 33 and 236 ± 27 vs. 208 ± 29 W; resting Sp_{O_2}, 98 ± 2 vs. 92 ± 4 and 98 ± 1 vs. 94 ± 3%; end-exercise Sp_{O_2}, 93 ± 5 vs. 81 ± 4 and 93 ± 3 vs. 81 ± 5%.	
Fukuda et al. (16)	Design: Randomized, controlled crossover trial. The subjects performed maximal exercise testing under normoxic (FI_{O_2}:0.21) and hypoxic (FI_{O_2}: 0.144) conditions. Setting: Normobaric hypoxia altitude simulation (FI_{O_2} 0.144).	1b	9	Healthy men (age 26.9 ± 1.5 yr) without any symptoms or evidence of significant disease	Time at altitude: Exposure to normobaric hypoxic gas mixture contacting 14.4% O_2 (corresponding to 3,000 m ASL) for ~30–45 min. Performance maximal exercise: Normoxia (FI_{O_2} 0.21) vs. hypoxia (FI_{O_2} 0.144); $\dot{V}O_2$ 3,039 ± 133 vs. 2,761 ± 99 ml/min; CO 30.2 ± 1.8 vs. 26.7 ± 2.1 l/min; stroke volume 163 ± 11 vs. 145 ± 11 ml; and Sp_{O_2} 96 ± 1 vs. 82 ± 1%, $P < 0.05$.	

Continued

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Table A2.—*Continued*

Reference	Design and Setting	EBM	*N*	Participants	Main Results	Comments
Sinha et al. (58)	Design: Two-arm parallel, randomized control trial. Daily physical exercise training at either SL or HA. The study contained 3 groups: lowlanders at low-land (SL-SL), lowlanders to HA (SL-4,650 m), and highlanders to HA (3,800 m/4,000 m–4,850 m). Setting: Field study at low land and 4,650 m in India.	1b	30	Healthy men from the Indian Army. Two groups living at SL (26.9 ± 5.2 and 28.1 ± 4.4 yr old) and one group living at HA (25.1 ± 7.6 yr old), between 3,800 and 4,000 m ASL	Time at altitude: 7 days of acclimatization at 3,500 m asl and 4 wk at 4,650 m asl. Performance at maximal exercise: Significant higher $\dot{V}O_{2max}$ in highlanders compared with lowlanders at HA and significant lower $\dot{V}O_{2max}$ in lowlanders at HA compared with lowlanders at low altitude.	The study contains only information on $\dot{V}O_{2max}$ and maximal exercise capacity.
Squires and Buskirk (60)	Design: Randomized, controlled, blinded trial. Treadmill exercise test was performed in ambient altitude (362 m) and at 914, 1,219, 1,524, and 2,268 m above SL. Setting: Simulated altitude hypobaric chamber.	0.1b	12	Healthy, physically active men	Time at altitude: 1–2 h of exposure to each altitude in the protocol using a hypobaric chamber. Performance submaximal exercise: $\dot{V}O_2$ was lower than the control at 2,286 m (3.5 ± 0.11 and 3.7 ± 0.09 l/min, $P <$ 0.01). Subjects with higher aerobic capacities expressed per unit body weight exhibited smaller decrements in $\dot{V}O_2$ than subjects with lower aerobic capacity did. Performance maximal exercise: With a test correlation of $r = 0.92$, $\dot{V}O_{2max}$ decreased from control values with incremental altitude, with a significant reduction of 0.21 l/min at 1,219 m. From 1,524 m to baseline was the reduction of 6.9% and from 2,286 m, 11.9%.	
				Exercise under hyperoxia in healthy individuals		
Ulrich et al. (68)	Design: Randomized, single-blinded crossover study. Four exercise tests (2 constant-load 75% W_{max} and 2 maximum workload tests) were performed to exhaustion, randomly ordered to either normoxia or hyperoxia (FI_{O_2}: 0.5). Setting: Hyperoxia with FI_{O_2} 0.21 vs. 0.5 via mouthpiece.	1b	32	Healthy volunteers (42 ± 15 yr, 12 women)	Performance W_{max}: The final 15 s of ramp exercise with FI_{O_2} 0.5 and FI_{O_2} 0.21 were compared. Under hyperoxia, W_{max} and Sp_{O_2} as well as cerebral tissue oxygenation were higher (270 ± 80 vs. 257 ± 76 W, 99 ± 1 vs. 96 ± 3, and 67 ± 9 vs. 61 ± 9%, respectively). Performance submaximal workload: In constant load, exercising under hyperoxia was longer than in normoxia (16 min 22 s ± 7 min 39 s vs. 10 min 47 s ± 5 min 58 s), whereas $\dot{V}E$ was lower in hyperoxia (82 ± 18 vs. 93 ± 23 l/min).	

Continued

Table A2.—*Continued*

Reference	Design and Setting	EBM	*N*	Participants	Main Results	Comments
Oussaidene et al. (42)	Design: Randomized, double-blinded crossover trial. Each participant performed two randomized exhaustive ramp exercises under normoxic or hyperoxic conditions. Setting: Hyperoxia provided by FI_{O_2} 0.3 via mouthpiece.	1b	8	Untrained men (age 27 ± 6 yr)	Performance maximal exercise: Power output (W_{max} = 302 ± 20 vs. 319 ± 28 W) and Sp_{O_2} (= 95.7 ± 0.9 vs. 97.0 ± 0.5%) at maximal exercise were increased by hyperoxia ($P < 0.05$). The muscular oxygenation change did not significantly differ with hyperoxia. Respiratory compensation point (259 ± 17 vs. 281 ± 25 W) and CO threshold (259 ± 23 vs. 288 ± 30 W) were improved ($P < 0.05$) with hyperoxia.	
Grataloup et al. (20)	Design: Randomized, single-blinded crossover trial. Ergometer ramp protocol to exhaustion under normoxic (0.21%) or hyperoxic (0.3%) conditions was performed in subjects exhibiting EIH and those who do not. Setting: Laboratory study with FI_{O_2} 0.21 vs. 0.3.	1b	16	Competing male cyclists (9 with Sa_{O_2} desaturation > 5%; 7 with less desaturation)	Performance maximal exercise: $\dot{V}O_{2max}$ improved with hyperoxia in exercise desaturators (EIH) and nondesaturators, but to a higher degree for EIH (12.8 ± 5.7 vs. 4.2 ± 4.6%, $P < 0.01$; means ± SD). Maximal power improved by 3.3 ± 3.3% ($P < 0.01$), regardless of the group.	
Prieur et al. (48)	Design: Randomized, single-blinded crossover trial. Each subject performed each exercise test under normoxic and hyperoxic conditions (FI_{O_2}: 0.3). The participants performed incremental exercise test and constant work rate exercise test at W_{max} (40, 55, 70, and 85%) for 12 min. Settings: Laboratory study with FI_{O_2} 0.21 and 0.3.	1b	10	Healthy male volunteers	Performance maximal exercise: $\dot{V}O_{2max}$ was significantly improved by 15.0 (15.2%) under hyperoxia, whereas performance (W_{max}) was improved by only +4.5 (3.0%). During incremental exercise, the slope of the linear regression relating $\dot{V}O_2$ to work rate was significantly steeper in hyperoxia than in normoxia [10.80 (0.88) vs. 10.06 (0.66) ml·min^{-1}·W^{-1}]. Performance submaximal exercise: During constant exercise tests, $\dot{V}O_2$ under hyperoxic conditions was higher in any %W_{max} protocol, and $\dot{V}O_2$ slow component was higher at 85% W_{max}.	

Continued

Table A2.—*Continued*

Reference	Design and Setting	EBM	*N*	Participants	Main Results	Comments
				Exercise under hyperoxia in patients with PAH or CTEPH		
Ulrich et al. (69)	Design: Randomized, sham-controlled, single-blinded crossover trial. Four exercise tests (2 constant-load 75% W_{max} and 2 W_{max} tests performed to exhaustion). Randomly ordered to either normoxia or hyperoxia (FI_{O_2}: 0.5). Setting: Hyperoxia with FI_{O_2} 0.21 vs. 0.5 via mouthpiece.	1b	22	Stable patients diagnosed with PAH or CTEPH with a resting Pa_{O_2} ≥ 7.3 kPa under PH-targeted drug therapy (8 women, mean age 61 yr, SD 14 yr).	Ramp exercise: Maximal work rate increased from 113 ± 38 W with normoxia to 132 ± 48 W under hyperoxia; mean difference was 19.7 W (95% CI: 10.5–28.9 W), $P < 0.001$. Constant-load exercise: Endurance increased from 571 ± 443 to 1,242 ± 514 s; mean difference was 671 s (95% CI 392–951 s), $P < 0.001$. Under hyperoxia, at end exercise, PA_{O_2}, cerebral and quadriceps muscle tissue oxygenation, and PA_{CO_2} were increased, and ventilatory equivalents for CO_2 were reduced, whereas physiological dead space/tidal volume ration remained unchanged.	

This table lists references retrieved by a MedLine/PubMed search performed on March 27, 2017, according to the criteria outlined in Table A1. No studies on effects of hypoxia on patients with pulmonary artery (PAH) or chronic thromboembolic pulmonary hypertension (CTEPH) were identified. SL, sea level; ASL, above sea level; HA, high altitude; EBM, evidence-based medicine (if the mentioned randomized controlled trial is the first published in this particular topic, then the evidence level 1b is present); EIH, exercise-induced arterial hypoxemia; CI, confidence interval; CO, cardiac output; P-Vo_{2peak}, power output corresponding to peak Vo_2 (in W).

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